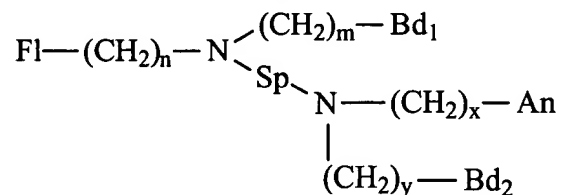


All five independent claims, 1, 14, 21, 52, and 59, require a modular fluorescence sensor having the following general formula:



wherein Fl is a fluorophore; Bd₁ and Bd₂ are independently selected binding groups, wherein the binding groups are capable of binding an analyte molecule to form a stable 1:1 complex; Sp is an aliphatic spacer; and An is an anchor group for attaching the sensor to a solid substrate; and n = 1 or 2, m = 1 or 2, and x is an integer.

The fluorescent sensor of the instant invention has a unique asymmetrical structure, which allows the spatial separation of bulky fluorophore and binding groups from the anchor group. Such an arrangement facilitates covalent attachment of the sensor to a variety of solid substrates (page 6, lines 4-6, of the instant specification).

The Examiner conceded that neither of the cited references, when considered alone, teaches the instant sensor, but relied on their combination for teaching the same. The Examiner appears to believe that it is obvious to attach the anchor group of the '954 patent to the amine group of the Sandanayake sensor to arrive at the sensor of the present invention. The Examiner alleges that such a combination is obvious because the '954 patent states that "In order to use the amplification components for analyte sensing in vivo, the components for the reaction must be immobilized in a polymer matrix that can be implanted subdermally." Applicants respectfully disagree.

It is respectfully submitted that nothing in either the '954 patent or the Sandanayake reference suggests the desirability (and thus the obviousness) of making the combination of elements proposed by the Examiner. Nothing in the '954 patent, including the statement quoted by the Examiner, suggests the desirability of replacing a single glucose-binding group of the fluorescent compound described in

the '954 patent with a cleft comprising two boronic acid moieties of the Sandanayake reference to arrive at the present invention. Similarly, nothing in the Sandanayake reference suggests the desirability of adding an anchor group of the '954 patent to the sensor (2) of the Sandanayake reference, let alone replacing one of the fluorophores with the anchor group, in order to arrive at the present invention.

Moreover, not only does the Sandanayake reference have no teaching of the desirability of attaching an anchor to the amino group of the sensor, but also the Sandanayake reference discourages such a modification. The Sandanayake reference teaches a symmetrical fluorescent sensor (2) which contains two boronic acid moieties for binding glucose and two pyrene units serving as fluorophores (page 503, right column). The reference teaches that such a symmetrical molecule provides high fluorescence switch-on factors and a high stability constant. In addition, the reference observes that a monomeric sensor (3) with a single boronic acid moiety and a single pyrene fluorophore has a low switch-on factor and a low stability constant. Accordingly, based on the fact that the symmetrical sensor (2) with two fluorophores produces superior results as compared to an asymmetrical sensor (3) with a single fluorophore, one skilled in the art would have been discouraged to eliminate one of the fluorophores from the sensor (2), let alone to replace the fluorophore with another functional group.

Therefore, applicants respectfully submit that the suggestion for the combination of the two references proposed by the Examiner comes only from the claimed invention itself. The skilled artisan would not have found it obvious to selectively pick and choose the separate elements and concepts from the '954 patent and the Sandanayake reference so as to arrive at the claimed invention without using the present claims as a guide. Such hindsight reconstruction of the invention is not a proper criteria for determining obviousness. There must be some reason or suggestion in either the '954 patent or the Sandanayake reference for selecting and combining the elements as proposed, other than the knowledge learned from the applicants' disclosure. Interconnect Planning Corporation v. Feil, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985). Thus, it is respectfully submitted that the ordinarily skilled

artisan, working without the benefit of the applicants' specification, would have had no motivation to combine the features of the cited references to arrive at the present claims 1-21, 52-56, 59, and 60.

Furthermore, the present invention provides a sensor with unexpectedly improved properties over the Sandanayake reference. Although the symmetrical sensor (2) of the Sandanayake reference is stable and provides a high fluorescent signal, the sensor (2) has a rigid and bulky structure unsuitable for attachment to surfaces and for use in heterogenic assays. The instant asymmetrical modular sensor, on the other hand, unexpectedly provides structural flexibility that allows the incorporation of an anchor group without sacrificing the fluorescent properties of the sensor. In this regard, applicants would like to draw the Examiner's attention to Figure 2 of the present invention and Figure 1 of the Sandanayake reference. A comparison of the two figures reveals that the sensor of the present invention with a single fluorophore has the same fluorescent spectra and peak separation as the sensor (2) of the Sandanayake reference having two fluorophores. Therefore, the sensor of the present invention advantageously provides structural flexibility combined with the desired fluorescent properties. This advantage is unexpected in view of the cited references. Because the Sandanayake reference teaches superior fluorescent properties of a symmetrical sensor with two fluorophores over an asymmetrical sensor with a single fluorophore, one skilled in the art would not have been motivated to eliminate one of the fluorophores from Sandanayake's sensor to arrive at the asymmetrical sensor of the present invention.

Thus, the Sandanayake reference and the '954 patent do not teach or suggest claims 1, 14, 21, 52, and 59 directed to the sensor of the present invention. Claims 2-13, 15-20, and 60 depend, directly or indirectly, from patentable claims 1, 14, 21, 52, and 59 and are, therefore, believed to be patentable for at least the same reasons as those claims.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number (213) 337-6700 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
HOGAN & HARTSON L.L.P.

Date: September 4, 2001

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